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Failure to Warn Products Liability for Manufacturers of FDA-Approved Drugs

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FAILURE TO WARN PRODUCTS LIABILITY
FOR MANUFACTURERS OF FDA-APPROVED DRUGS
by
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Submitted in partial fulfillment of the requirements of the
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Professor Neal Fortin
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INTRODUCTION

Currently, "failure to warn" product liability claims are among the most common type of claims brought by patients who have been injured as a result of taking pharmaceutical products.¹

In a claim for failure to warn, the patient attempts to hold the drug manufacturer liable for side effects caused by the drug under the theory that the drug is defective because its labeling did not

¹ RESTATEMENT (THIRD) OF TORTS: PROD. LIAB. § 6, cmt d (1998); *see also* Viscusi et al., *The Effect of Products Liability Litigation on Innovation: Deterring Inefficient Pharmaceutical Litigation: an Economic Rationale for the FDA Regulatory Compliance Defense*, 24 SETON HALL L. REV. 1437, 1463 (1994).

adequately warn the patient or the patient's physician of the potential for the side effect's occurrence.² Cases against pharmaceutical companies for failure to warn of side effects are different than most failure to warn tort cases because the labeling that accompanies prescription drugs is heavily monitored and must be approved by a federal agency, the Food and Drug Administration ("FDA").³ The FDA has created a complete web of regulations controlling the information that must be presented on the labeling, how the information must be gathered, and the presentation and format that must be used.⁴

States must decide whether to hold pharmaceutical companies liable for labeling that has been approved by a federal government agency and what effect the agency's approval will have in state tort cases. Although many states focus on the economic ramifications of tort liability protection, it seems the most appropriate question for states and commentators to ask is whether the FDA approval process is rigorous and scientifically based, such that FDA approval of the drug warrants a presumption of innocence for the drug's manufacturer. After all, if drug manufacturers are presumed to have adequately warned the public, then the concern should be focused not only on the economics of enforcement, but also on whether the manufacturers have actually warned the public.

State legislatures, rather than state courts, are the appropriate bodies to determine how FDA-approved drugs and drug labeling will be treated in failure to warn tort suits. A legislative body is able to consult independent scientists to explain the scientific validity of FDA drug approval, where courts are constrained to the facts that are presented in a given case or

² RESTATEMENT (THIRD) OF TORTS: PROD. LIAB. § 6(b)(3), (d)(1)-(2) (1998).

³ Drugs: General, 21 C.F.R. §§ 201.56-201.57 (2007); *see also* Drugs for Human Use, 21 C.F.R. § 314.107(a) (2007) ("A drug product may be introduced or delivered for introduction into interstate commerce when approval of the application . . . for the drug product becomes effective."); Drugs for Human Use, 21 C.F.R. § 314.125(b)(3)-(6), (8), (15) (2007) (providing label-related reasons that the FDA can refuse to approve a drug product).

⁴ 21 C.F.R. §§ 201.56-201.57.

controversy. Legislatures are also better equipped than courts to make policy judgments because the legislature is able to consider the matter as a whole, rather than in relation to a specific case, and because legislatures are politically accountable to their constituents.

Many state legislatures have already addressed the issue of drug manufacturer tort liability, and they have proposed varying solutions to the problem of state law tort liability for federally approved drug product labeling. As a result, some state legislatures have provided strong protection against failure to warn tort suits involving FDA-approved drug products, while other states have provided much less protection.⁵ There are three primary views regarding the interplay between the federal law governing pharmaceutical drug approval and state product liability tort suits. First, states may provide drug manufacturers with immunity from tort suits if the drug's labeling has been approved by the FDA.⁶ Second, states may provide partial protection to drug manufacturers by legislating a rebuttable presumption in the drug manufacturer's favor, by eliminating punitive damages, or by requiring the plaintiff to meet a higher burden of proof in tort suits attacking FDA-approved labeling.⁷ Alternatively, states may

⁵ Compare MICH. COMP. LAWS ANN. § 600.2946(5) (West 2007) (providing that drug product labeling cannot be defective if it has been approved by FDA) and N.J. STAT. ANN. § 2A:58C-4 (West 2007) (providing rebuttable presumption that drug product's FDA-approved warning is adequate) and N.J. STAT. ANN. § 2A:58C-5(c) (West 2007) (barring punitive damages for FDA-approved labeling if the manufacturer has not knowingly withheld information or misled the FDA) and OHIO REV. CODE ANN. § 2307.80(C)(1) (West 2007) (barring punitive damages for FDA-approved labeling unless there is a showing by the preponderance of the evidence that the manufacturer misled the FDA) and OR. REV. STAT. ANN. § 30.927 (West 2007) (barring punitive damages for FDA-approved labeling) and OR. REV. STAT. ANN. § 30.730(1) (West 2007) (requiring clear and convincing evidence of malice or "reckless and outrageous indifference to a highly unreasonable risk" before punitive damages may be awarded in civil actions) and TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a) (2006) (providing rebuttable presumption that drug manufacturer not liable for failure to warn if the labeling accompanying the drug product was approved by the FDA) and UTAH CODE ANN. § 78-18-2 (West 2007) (barring punitive damages if the relevant drug was approved by the FDA absent clear and convincing evidence that the manufacturer knowingly withheld material evidence from the FDA) with *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981) (appeal from New Hampshire case where treatment of drug manufacturer's liability for failure to warn was evaluated according to products liability standards).

⁶ See, e.g., MICH. COMP. LAWS ANN. § 600.2946(5) (West 2007).

⁷ See, e.g., N.J. STAT. ANN. § 2A:58C-4 (West 2007); N.J. STAT. ANN. § 2A:58C-5(c) (West 2007); OHIO REV. CODE ANN. § 2307.80(C)(1) (West 2007); OR. REV. STAT. ANN. § 30.927 (West 2007); OR. REV. STAT. ANN. § 30.730(1) (West 2007); TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a) (2006); UTAH CODE ANN. § 78-18-2 (West 2007).

permit suits against pharmaceutical manufacturers to proceed in the same manner as any other failure to warn tort suit.⁸

The FDA's official position, as explained in the preamble to its final labeling rule published on January 24, 2006, is that the FDA labeling rules preempt conflicting state law.⁹ Some commentators have also argued, based on general principles of federal preemption or based on an economic rationale, that FDA regulations governing the labeling of pharmaceutical products should preempt state "failure to warn" tort claims, such that compliance with the FDA's rules creates a presumption of innocence.¹⁰ However, in evaluating whether drug manufacturers are entitled to protection from tort liability, the most reasonable approach for the legislatures to take is to, first, attempt to understand the process of FDA approval and continued monitoring of drug products. Then, the legislators should question and evaluate whether the FDA approval process justifies the assumptions that are inherent in a decision to grant tort liability protection for drug manufacturers.

I. PRELIMINARY INVESTIGATION OF DRUG PRODUCTS

Individual drug developers spend significant amounts of time and money trying to identify and develop drug products that will be effective at treating disease and that will be profitable. The FDA regulates even some of the preliminary steps in the identification and pre-

⁸ See *Brochu v. Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981) (New Hampshire law).

⁹ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products. 71 Fed. Reg. 3922, 3933-34 cmt. 13 (Jan. 24, 2006) (stating FDA's position on preemptive power of its regulations over state law). If the federal regulations preempt state law, state regulations may be immaterial in failure to warn products liability cases. However, this article will address the policy concerns of the states and state lawmakers. Preemption is distinct from the question of state law and is a matter of federal law. However, the effect of preemption is that the state laws with requirements different than the federal law would not be enforced.

¹⁰ Howard L. Dorfman, Vivian M. Quinn, Elizabeth A. Brophy, *Presumption of Innocence: FDA's Authority to Regulate the Specifics of Prescription Drug Labeling and the Preemption Debate*, 61 FOOD AND DRUG L.J. 585 (2006); Viscusi et al., *The Effect of Products Liability Litigation on Innovation: Detering Inefficient Pharmaceutical Litigation: an Economic Rationale for the FDA Regulatory Compliance Defense*, 24 SETON HALL L. REV. 1437, 1463 (1994).

clinical testing to ensure that there is an adequate scientific basis for the drug manufacturer to determine that the drug product is ready to be used in a clinical investigation.

A. Drug Manufacturer Identification of Potential New Drug Products

Pharmacology and toxicology testing are used to identify potentially useful pharmaceutical products through nonclinical animal or in vitro testing.¹¹ The sponsor of the testing, generally a drug manufacturer, must submit this nonclinical test data to the FDA in an Investigational New Drug application ("IND") before any clinical testing of the proposed drug product may begin.¹² The pharmacology information submitted in the IND must include the drug's mechanism of action, and, *if it is known*, "information on the absorption, distribution, metabolism, and excretion of the drug."¹³

The toxicology report submitted to the FDA in the IND must be more detailed than the pharmacology report. A toxicology report contains information regarding the acute toxicity, chronic toxicity and toxicity to the reproductive system or fetus and may include information specific to the method of drug delivery.¹⁴ The toxicology report is the primary basis for determining that a drug is safe enough to initiate clinical trials using human subjects.¹⁵ Therefore, the nonclinical toxicology testing that is necessary "depend[s] on the nature of the

¹¹ Drugs for Human Use, 21 C.F.R. § 312.23(a)(8) (2007). The FDA has promulgated regulations controlling procedures that must be used during the nonclinical testing, the good laboratory practice ("GLP") guidelines, so that the testing is performed pursuant to quality standards. § 312.23(a)(8)(iii).

¹² 21 C.F.R. § 312.23(a)(8).

¹³ 21 C.F.R. § 312.23(a)(8)(i)(a), (b).

¹⁴ 21 C.F.R. § 312.23(a)(8)(ii)(a).

¹⁵ See U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 13-14 (1995).

drug and the phase of human investigation"¹⁶ and the report must include a summary of information and supporting data sufficient for the FDA to perform a detailed review.¹⁷

Along with the toxicology data, the drug manufacturer must include the identification and qualifications of those employees or consultants of the sponsor who "evaluated the animal safety data and concluded that it [was] reasonably safe to begin the proposed human study" based on the toxicology data collected.¹⁸

B. Clinical Investigation of the Drug Product

Clinical investigation must be carried out before the drug can be marketed in the United States.¹⁹ Clinical investigation of the drug product is carried out in three phases defined by the FDA as Phase 1, Phase 2, and Phase 3.²⁰ Clinical investigations are intended to "distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."²¹ The clinical investigations are used to gather evidence that the drug product is effective for the claimed indications and that the drug is reasonably safe. In order to provide the necessary "substantial evidence" that the drug product is effective for the claimed indications, the sponsor must perform adequate and well-controlled investigations.²² These investigations must be described in the IND submitted to the FDA.²³

¹⁶ *Id.* at 11.

¹⁷ Drugs for Human Use, 21 C.F.R. § 312.23(a)(8)(ii) (2007). At the time of IND submission, the sponsor may submit an integrated summary report of unaudited toxicology findings, but fully quality-assured documents should be available for FDA review within 120 days after the human trials begin. U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 12 (1995).

¹⁸ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 14 (1995).

¹⁹ Drugs for Human Use, 21 C.F.R. § 314.107(a) (2007).

²⁰ Drugs for Human Use, 21 C.F.R. § 312.21 (2007).

²¹ Drugs for Human Use, 21 C.F.R. § 314.126(a) (2007).

²² *Id.*

²³ Drugs for Human Use, 21 C.F.R. § 312.23(a)(6) (2007); *see also infra* Part I.B.3.

1. Drug Companies' Clinical Investigation Responsibilities

The sponsor for the FDA-mandated clinical investigations and FDA approval process is usually the applicant who submitted the IND and who will later submit the New Drug Application ("NDA"). This sponsor is generally the drug company that is aiming to commercialize a drug product. Sponsors' responsibilities are explicitly stated in the FDA's rules, and include: selecting qualified investigators and monitors for the clinical investigations, ensuring that the investigations are properly monitored and that they are in accordance with the IND, controlling access to the drug, and ensuring that the FDA and all investigators are informed of adverse events or newly discovered risks associated with the drug.²⁴ The sponsor has the obligation to discontinue investigations and notify the FDA if it determines "that its investigational drug presents an unreasonable and significant risk to subjects."²⁵ The sponsor is also required to maintain records tracking the financial interest that investigators may have in the drug for two years after the NDA is approved.²⁶ These records must be made available to FDA personnel upon request.²⁷

The sponsor may or may not act as the actual clinical investigator.²⁸ Investigators are responsible for ensuring the clinical investigation is conducted according to the written investigational plan, the drugs being administered to the subjects are properly controlled, the appropriate informed consent is granted by each human patient, and "adequate records" of drug use in the study are kept.²⁹ The investigator is also required to monitor the subjects' experiences with the drug and maintain a proper case history for each patient who is administered the drug.³⁰

²⁴ Drugs for Human Use, 21 C.F.R. § 312.50 (2007); Drugs for Human Use, 21 C.F.R. § 312.53(a), (b), (d) (2007).

²⁵ Drugs for Human Use, 21 C.F.R. § 312.56 (2007).

²⁶ Drugs for Human Use, 21 C.F.R. § 312.57(a)-(c) (2007).

²⁷ Drugs for Human Use, 21 C.F.R. § 312.58(a) (2007)

²⁸ See Drugs for Human Use, 21 C.F.R. § 312.70 (2007).

²⁹ Drugs for Human Use, 21 C.F.R. § 312.60, 21 C.F.R. 312.62(a) (2007).

³⁰ Drugs for Human Use, 21 C.F.R. § 312.62(b) (2007).

Further, the investigator must report all relevant information to an Institutional Review Board, including proposed changes in protocol or unexpected events.³¹ Investigators, like sponsors, are required to provide the FDA access to review records³² and they can be disqualified if they "repeatedly or deliberately fail[] to comply with the [FDA's] requirements."³³

During Phase 1 the manufacturer's and the FDA's primary concern is assuring the subjects' safety and their rights.³⁴ Phase 1 testing requirements are often flexible, and the FDA recognizes that Phase 1 is often a learning tool for the drug's sponsor. The aim of testing in Phase 1 is to evaluate "the metabolism and pharmacologic actions of the drug . . . , the side effects associated with increasing doses, and, if possible, to gain early evidence of effectiveness."³⁵ To this end, the drug may be given to patients with the condition the drug is intended to treat or to a small group of healthy adults.³⁶ The FDA recommends a general sample size of only twenty to eighty subjects in Phase 1 trials.³⁷

The scientific basis for Phase 2 studies must be progressively stronger than that required for Phase 1 investigations.³⁸ There must be a strong enough scientific underpinning for the studies so that at the conclusion of Phase 2 trials the sponsor is able to show "preliminary evidence suggesting effectiveness of the drug."³⁹ During Phase 2 investigations, the drug is given to a small group of persons affected by the drug's targeted illness or condition, usually no more than a few hundred subjects.⁴⁰ Then, the drug product's effects on the illness and its side

³¹ Drugs for Human Use, 21 C.F.R. § 312.66 (2007).

³² Drugs for Human Use, 21 C.F.R. § 312.68 (2007).

³³ Drugs for Human Use, 21 C.F.R. § 312.70(b) (2007).

³⁴ Drugs for Human Use, 21 C.F.R. § 312.22(a) (2007).

³⁵ Drugs for Human Use, 21 C.F.R. § 312.21(a) (2007).

³⁶ *Id.*

³⁷ § 312.21(a).

³⁸ § 312.21(a) ("sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid Phase 2 studies").

³⁹ § 312.21(c).

⁴⁰ § 312.21(b).

effects must be monitored, evaluated, and analyzed by the investigator according to the investigation protocol's parameters.⁴¹

Phase 3 testing allows more data on safety and effectiveness to be collected by providing the drug product to a larger sample of patients who are clinically affected with the condition the drug is intended to treat.⁴² There is an even greater emphasis on the scientific evaluation of the drug in the final phase of the testing to ensure that there will be sufficient evidence for the FDA to evaluate the drug product⁴³ and its "overall benefit-risk relationship" as necessary for FDA approval of the drug product.⁴⁴ Importantly, the Phase 3 scientific evidence also provides the basis for the required labeling of the drug product, which the FDA must approve before the drug product can be marketed in the United States.⁴⁵

2. FDA Monitoring of Clinical Investigations through IND Submission

The FDA uses the IND process to track the drug manufacturer's clinical investigations of drug products. The primary purpose of the IND is for the drug manufacturer to inform the FDA of its scientific research plan, which may be updated as the research progresses.⁴⁶ The initial IND must be submitted before a drug can be shipped in the United States or used in clinical investigations in the United States⁴⁷ and the "IND may be submitted for one or more phases of an

⁴¹ Drugs for Human Use, 21 C.F.R. § 312.21(b) (2007).

⁴² § 312.21(c).

⁴³ Drugs for Human Use, 21 C.F.R. § 312.22(a) (2007).

⁴⁴ § 312.21(c).

⁴⁵ § 312.21(c).

⁴⁶ § 312.22(c).

⁴⁷ § 312.22; U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 2-3 (1995).

investigation."⁴⁸ Thirty days after the FDA receives the initial IND from the sponsor, the sponsor may begin clinical testing, where the drug will be tested on human subjects.⁴⁹

The FDA has expressly prescribed the information that must be present in the IND and the form that must be used.⁵⁰ However, the drug sponsors are given wide latitude in determining the content of the submission within the categories mandated by the FDA and are expected to tailor their submissions to the specific scientific needs of the drug being tested.⁵¹ The amount of information required by the FDA can vary according to many factors including the drug's novelty, "the known or suspected risk" of the drug, and its phase of development.⁵² Further, according to the FDA, there is a current concentration on "increasing the efficiency of . . . the drug development process without sacrificing the [FDA's] long-standing safety and efficacy standards."⁵³ To further this goal, the FDA has released guidance documents intended to help drug sponsors fully appreciate the "flexibility in the amount and depth of various data to be submitted in an IND" to help improve efficiency in the initial stage of IND testing.⁵⁴

An IND submitted to the FDA must contain a protocol for each study that is planned or that will be carried out during the clinical investigations.⁵⁵ However, the clinical testing

⁴⁸ Drugs for Human Use, 21 C.F.R. § 312.21 (2007).

⁴⁹ Drugs for Human Use, 21 C.F.R. § 312.40(a)-(b) (2007), *see also* U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, IND PROCESS AND REVIEW PROCEDURES (INCLUDING CLINICAL HOLDS), MANUAL OF POLICIES AND PROCEDURES 6030.1, 2 (1998). The FDA policy is to review the sponsor's initial IND and notify the sponsor within thirty days if a clinical hold will be placed. *Id.* at 3. A "clinical hold" is an FDA order to "delay a proposed clinical investigation or suspend an ongoing investigation." Drugs for Human Use, 21 C.F.R. § 312.42(a) (2007).

⁵⁰ Drugs for Human Use, 21 C.F.R. § 312.23 (2007).

⁵¹ Drugs for Human Use, 21 C.F.R. § 312.22(d) (2007). However, the FDA requires any relevant information to the IND to be supplied by the applicant upon request. § 312.23(a)(11).

⁵² § 312.22(b). The initial IND is not expected to contain the same level of detail that is necessary before marketing approval. U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, IND PROCESS AND REVIEW PROCEDURES (INCLUDING CLINICAL HOLDS), MANUAL OF POLICIES AND PROCEDURES 6030.1, 4 (1998).

⁵³ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 1 (1995).

⁵⁴ *Id.* at 1-2.

⁵⁵ § 312.23(a)(6).

protocols submitted for Phase 1 investigations are not required to include as much detail as Phase 2 or Phase 3 protocols.⁵⁶ During Phase 1 the manufacturer's and the FDA's focus should be primarily on the safety of subjects.⁵⁷ The FDA has, therefore, specified grounds that will justify a clinical hold order on an investigation which vary depending on the phase of the investigational process.⁵⁸ During Phase 1 the FDA can place a clinical hold if the subjects would be "exposed to an unreasonable and significant risk of illness or injury"; if the IND lacks sufficient information to assess the subjects' risks; if the study calls for a drug to be tested only with one gender and the disease it is intended to treat affects both genders; or if the investigators are unqualified or insufficiently informed.⁵⁹

IND protocols submitted for Phase 2 and Phase 3 investigations should specify the full details of the proposed investigations, including alternatives or contingencies that may be required for scientific or safety reasons.⁶⁰ Additionally, due to the increasing burden to provide scientifically-based data, during Phase 2 and Phase 3 the FDA may place a clinical hold on an investigation for any of the reasons listed for Phase 1 *or* if the planned investigation is "clearly deficient in design."⁶¹

Unless clinical test subjects face an "immediate and serious risk" the FDA will attempt to resolve any deficiency in the proposed or ongoing study through discussion with the drug's

⁵⁶ *Supra* note 33 at 4.

⁵⁷ Drugs for Human Use, 21 C.F.R. § 312.23(a)(6)(i) (2007) (only elements which are critical to safety, such as "necessary monitoring of vital signs and blood chemistry" need be included in detail); U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 4 (1995).

⁵⁸ Drugs for Human Use, 21 C.F.R. § 312.42(b)(1)-(2) (2007).

⁵⁹ § 312.42(b)(1).

⁶⁰ Drugs for Human Use, 21 C.F.R. § 312.23(a)(6)(ii) (2007).

⁶¹ § 312.42(b)(2).

sponsor before making a clinical hold order.⁶² FDA personnel's discussions with the sponsor about such matters must be approved by an FDA team leader and documented appropriately.⁶³ Further, if a clinical hold is imposed, the Division Director of the FDA must be involved.⁶⁴

In addition to the clinical investigations that must be carried out pursuant to the IND, the IND applicant is also required to "promptly" review all safety information it obtains.⁶⁵ After review, the IND applicant must submit a written IND safety report to the FDA and any participating investigator if there is either a serious *and* unexpected adverse experience or a finding from laboratory animal studies suggesting a significant risk for human "mutagenicity, teratogenicity, or carcinogenicity."⁶⁶ The sponsor of the IND is also required to submit an annual report describing the progress of the investigation.⁶⁷ The annual report should include a summary of the year's clinical and nonclinical findings; a summary of the "most serious adverse experiences"; a list of clinical study subjects who have died in the previous year or who dropped out of clinical studies due to adverse events; and a summary of significant changes in the manufacture of the drug that have taken place in the previous year.⁶⁸ The sponsor is also required to provide an updated plan for the coming year in the IND annual report.⁶⁹

⁶² § 312.42(c). If the FDA determines that a clinical hold is necessary, it's policy is to first attempt to resolve the issue with the sponsor, and if it cannot do so, inform the sponsor of the specific reasons for the clinical hold. U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, IND PROCESS AND REVIEW PROCEDURES (INCLUDING CLINICAL HOLDS), MANUAL OF POLICIES AND PROCEDURES 6030.1, 3 (1998).

⁶³ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, IND PROCESS AND REVIEW PROCEDURES (INCLUDING CLINICAL HOLDS), MANUAL OF POLICIES AND PROCEDURES 6030.1, 3 (1998).

⁶⁴ *Id.*

⁶⁵ Drugs for Human Use, 21 C.F.R. § 312.32(b) (2007).

⁶⁶ § 312.32(c)(1)(i)(A), (B). The FDA must be notified within fifteen calendar days of the finding, or within seven calendar days if there is an unexpected fatal or life-threatening adverse reaction. § 312.32(c)(1)-(2).

⁶⁷ Drugs for Human Use, 21 C.F.R. § 312.33(a) (2007).

⁶⁸ § 312.33(b)(1), (3)-(4), (7).

⁶⁹ § 312.33(c).

3. FDA Requirement of Adequate and Well-Controlled Studies

The FDA requires adequate and well-controlled studies to be performed during the clinical investigations. The FDA has promulgated rules to define what will qualify as an "adequate and well-controlled study."⁷⁰ Compliance with these rules is measured using the FDA's expertise, rather than requiring strict adherence, so that the most scientifically appropriate or feasible methods can be used to evaluate a drug. However, the rules do set base-line requirements, such as the requirement that an adequate and well-controlled study have both a clear protocol and a post-study report.⁷¹

A protocol is a scientific plan for an individual clinical investigation. The protocol must describe: the purpose of the study and a description of the study's design; the subject selection criteria; the dosage of the drug that will be used; the observations and measurements that will be taken for the study; the clinical steps that will be taken to monitor the subjects and minimize risk to clinical subjects; and the qualifications of the investigators.⁷² The protocol should provide a study design which "permits a valid comparison with a control to provide a quantitative assessment of drug effect," including the method for selection of subjects with the indicated disease, a method of assessing the subject's response and criteria to judge the response, and measures that will be used to mitigate bias.⁷³ The post-study report should explain the methods of analysis actually used and provide an analysis of the data collected in the investigations that is "adequate to assess the effects of the drug."⁷⁴ Further, for any clinical investigation to be

⁷⁰ Drugs for Human Use, 21 C.F.R. § 314.126(b) (2007).

⁷¹ § 314.126(b)(1).

⁷² Drugs for Human Use, 21 C.F.R. § 312.23(a)(6)(iii) (2007).

⁷³ 314.126(b)(1)-(7). The Director of the Center for Drug Evaluation and Research may waive any of the controlled study requirements. § 314.126(c).

⁷⁴ § 314.126(b)(1)-(7).

considered adequate and well-controlled, the drug product provided to the test subjects must have had a standardized "identity, strength, quality, purity and dosage form."⁷⁵

There are several recognized methods of protocol design that permit an adequate control comparison.⁷⁶ In placebo concurrent control, the drug product is compared to a placebo, which is an inactive compound made to look like the drug product.⁷⁷ In dose-comparison studies at least two different doses of the drug are administered and the effects are compared.⁷⁸ Both the placebo concurrent control method and the dose-comparison method often use randomization and blinding to further eliminate bias and provide scientifically valid results.⁷⁹ Alternatively, the test drug product may be compared with no treatment or with another known effective therapy.⁸⁰ Also, under appropriate circumstances, the "results of treatment with the test drug may be compared with experience historically derived from the adequately documented natural history of the disease or condition."⁸¹

4. *Chemistry, Manufacturing, and Control Information in the IND*

An IND must also contain chemistry, manufacturing, and control ("CMC") information regarding the "proper identification, quality, purity, and strength of the investigational drug."⁸² The CMC must include a description of the drug substance itself, a description of the final drug product and its components, a general description of the composition and manufacture of any placebos that will be used, and the proposed labeling.⁸³

⁷⁵ § 314.126(d).

⁷⁶ Drugs for Human Use, 21 C.F.R. § 314.126(b)(2)(i)-(v) (2007).

⁷⁷ § 314.126(b)(2)(i).

⁷⁸ § 314.126(b)(2)(ii).

⁷⁹ § 314.126(b)(2)(i)-(ii).

⁸⁰ § 314.126(b)(2)(iii)-(iv).

⁸¹ § 314.126(b)(2)(v).

⁸² Drugs for Human Use, 21 C.F.R. § 312.23(a)(7) (2007).

⁸³ § 312.23(a)(7)(iv).

The FDA places an increasing burden on the drug manufacturer to provide information on the manufacturing process and on the quality of the final product as each phase of the investigation is undertaken.⁸⁴ The FDA recognizes that there will be development in the production methods throughout the nonclinical, clinical, and commercial production phases and requires the sponsor to update the IND description of manufacturing procedures as new methods are used.⁸⁵ However, there must be some consistency in the manufacturing methods and some indication that the advancing production methods are producing a product of the same identity, strength, quality, and purity as the product tested in earlier phases of the investigation.

In the initial phase there is an emphasis on ensuring that the raw materials are pure and correctly identified, but the FDA does not require complete and final specifications for the drug product until "the end of the investigational process."⁸⁶ For Phase 1 studies, the IND need include only "a brief description of the test methods used" and "[p]roposed acceptable limits supported by simple analytical data" for determining the identity, strength, quality, and purity of the drug substance and the drug product.⁸⁷ The FDA's policy is to "concentrate on determining if there are any reasons to believe the manufacturing or controls for the clinical trial product present unreasonable health risks to the subjects in the initial investigations."⁸⁸

⁸⁴ § 312.23(a)(7)(i); U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 4 (1995).

⁸⁵ § 312.23(a)(7)(i), (iii); U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 5 (1995).

⁸⁶ § 312.23(a)(7)(i).

⁸⁷ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS, 7, 9 (1995).

⁸⁸ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, IND PROCESS AND REVIEW PROCEDURES (INCLUDING CLINICAL HOLDS), MANUAL OF POLICIES AND PROCEDURES 6030.1, 4-5 (1998); *see also Id.* at 5.

As further clinical investigations of the drug product are carried out, the CMC provided by the manufacturer must be more detailed and must be developed in a manner that will be sufficient to support the NDA.⁸⁹ At each stage of development, or when there is a change in the drug substance, the manufacturing process, or the drug product formulation, the sponsor should evaluate whether "the changes can directly or indirectly affect the safety of the [drug] product."⁹⁰ If the change has "a significant potential to affect the safety of the product" CMC safety information should be submitted in an informational amendment to the IND.⁹¹

In Phase 2 of the clinical investigation more detailed information should be provided in the IND regarding the manufacturing, packaging, and tentative specifications for the drug substance.⁹² The composition of the drug product, control of excipients, and control of drug product should also be updated by the sponsor in an informational amendment before or during Phase 2 of the clinical investigation.⁹³ Additionally, before or during Phase 3 of the clinical investigations the sponsor should update this CMC information again.⁹⁴ The CMC section in the IND submitted for Phase 3 investigations should be progressively closer to the requirements for a New Drug Application and should contain considerably more detail than the usual Phase 1 IND.⁹⁵

⁸⁹ See U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, INDs FOR PHASE 2 AND PHASE 3 STUDIES: CHEMISTRY, MANUFACTURING AND CONTROLS INFORMATION, 3 (2003).

⁹⁰ *Id.* at 4.

⁹¹ *Supra* note 89, at 3.

⁹² *Supra* note 89, at 6-9.

⁹³ *Supra* note 89, at 10-13.

⁹⁴ *Supra* note 89, at 13-21.

⁹⁵ See *supra* note 89, at 13-21.

II. FDA APPROVAL OF NEW DRUG PRODUCTS

The FDA began the NDA approval process in 1938, and since that time, there has been an NDA submitted for every new drug product prior to its commercial sale.⁹⁶ Once the FDA approves an NDA, the drug product may be delivered "into interstate commerce."⁹⁷ The FDA's stated purposes in the NDA procedures are to "[f]acilitate the approval of drugs shown to be safe and effective" and to "ensure the disapproval of drugs not shown to be safe and effective."⁹⁸ During the NDA review, the FDA is concerned with (1) whether the drug is safe and effective for the proposed use, particularly, whether the benefits of the drug outweigh its risks, (2) whether the labeling contains all necessary information, and (3) whether the methods and controls of manufacturing are "adequate to preserve the drug's identity, strength, quality, and purity."⁹⁹ The NDA cannot be submitted until all phases of the clinical investigations have been completed because the information from the clinical investigations is required to support the evaluation of benefits and risks of the drug and also to determine the drug product's labeling.

A. General NDA Requirements

An NDA applicant may also seek a waiver for the submission of any section of the NDA or any requirement of postmarketing reporting,¹⁰⁰ or request that the FDA waive any statutory criteria for an adequate and controlled study.¹⁰¹ A request to waive compliance with NDA or post-marketing reporting requirements must include an explanation why compliance with the governing regulation is "unnecessary or cannot be achieved" and either a proposed alternative

⁹⁶ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *New Drug Application (NDA) Process, Introduction*, www.fda.gov/cder/regulatory/applications/NDA.htm#Introduction.

⁹⁷ Drugs for Human Use, 21 C.F.R. § 314.107(a) (2007).

⁹⁸ Drugs for Human Use, 21 C.F.R. § 314.2(a)-(b) (2007).

⁹⁹ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *Supra* note 96.

¹⁰⁰ Drugs for Human Use, 21 C.F.R. § 314.90(a) (2007). The applicant may also request a waiver of pediatric use information or testing. § 314.90(a)

¹⁰¹ § 314.90(a).

that "satisfies the purpose of the requirement" that the applicant is seeking waive or other information which the applicant believes justifies the waiver.¹⁰² The FDA will grant the waiver if compliance with the requirement is unnecessary under the circumstances, the proposed alternative satisfies the requirement, or "[t]he applicant's submission otherwise justifies a waiver."¹⁰³

If there is a change or discovery relevant to the NDA, the applicant is permitted to submit an amendment to an application that has been filed but is not yet approved.¹⁰⁴ If the change qualifies as a major amendment, it is considered by the FDA to be an agreement by the applicant to extend the regulatory timeframe for the FDA's decision whether to approve the application.¹⁰⁵ If the amendment is not considered a major amendment, it does not extend the period of review.¹⁰⁶ However, despite the 180-day regulatory timeframe for FDA review of drug products, the median time period for review of standard drugs in 2005 was 11.8 months and the median approval time was 13.1 months.¹⁰⁷

B. Required NDA Content

The NDA must include a significant amount of "summary" information for the FDA to review. The summary must be provided in "enough detail that the reader may gain a good general understanding of the data and information in the application" and is expected to contain "the level of detail required for publication in . . . refereed scientific and medical journals."¹⁰⁸ The NDA summary sections must include: the proposed labeling of the drug product; a

¹⁰² § 314.90(a)(1)-(3).

¹⁰³ § 314.90(b)(1)-(3).

¹⁰⁴ Drugs for Human Use, 21 C.F.R. § 314.60(a) (2007).

¹⁰⁵ *Id.*

¹⁰⁶ § 314.60(a).

¹⁰⁷ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *CDER 2005 Report to the Nation Available Data*, <http://www.fda.gov/cder/reports/rtn/2005/rtn2005%20accessible%20data.htm>.

¹⁰⁸ Drugs for Human Use, 21 C.F.R. § 314.50(c)(1) (2007).

designation of the pharmacologic class of the drug, "its intended use, and the potential clinical benefits of the drug product"; a description of the marketing history; summaries of several of the technical sections of the NDA; and a discussion of the "benefit and risk considerations related to the drug."¹⁰⁹ This summary information covers all of the primary areas of the NDA.

The NDA must also contain fully detailed technical sections in addition to the summary sections provided for FDA review. The technical sections must contain enough information and data for the FDA to become familiar with the drug product and "to make a knowledgeable judgment about whether to approve the application."¹¹⁰ The technical sections also provide the basis for all of the claims or statements that are in the summary sections of the NDA.

1. Pharmacology, Toxicology, Pharmacokinetics and Bioavailability Technical Sections

The NDA must include technical sections addressing nonclinical pharmacology, toxicology, human pharmacokinetics, and bioavailability.¹¹¹ The nonclinical pharmacology studies are pertinent because they provide preliminary evidence concerning how the drug is expected to work, what its proposed therapeutic properties are, what its potential adverse effects may be, and what quantity or dosing of the drug would be toxic to patients.¹¹² Some level of nonclinical testing must be performed before the clinical investigations begin to support the safety determinations permitting commencement of the clinical trials. However, the nonclinical investigations may be continued concurrently with the clinical trials¹¹³ and the pertinent results must be included in the NDA. Further, the results of human studies relating to the bioavailability

¹⁰⁹ § 314.50(c)(2)(i)-(ix).

¹¹⁰ § 314.50(d).

¹¹¹ § 314.50(d)(2)-(3).

¹¹² See § 314.50(d)(2)(i)-(ii).

¹¹³ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, M3 NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS FOR PHARMACEUTICALS, 2-3 (1997).

and pharmacokinetic properties of the drug must be described in the NDA, including a "description of the analytical procedures and the statistical methods used in each study."¹¹⁴

2. Clinical Data Technical Section

The clinical data section must describe all of the clinical investigations of the drug and must also briefly compare the clinical findings with the nonclinical findings so the FDA may determine whether the nonclinical studies provided an accurate scientific prediction.¹¹⁵ If there are any controlled studies that were not completed or were not analyzed in detail by the applicant, the reason for the lack of completion or analysis must also be explained in the NDA.¹¹⁶

The applicant must provide an "integrated summary" of the clinical data that demonstrates "substantial evidence of effectiveness for the claimed indications" and evidence "to support the dosage and administration section of the labeling."¹¹⁷ To facilitate review of the effectiveness information, it must be "presented by gender, age, and racial subgroups" and if there are other subgroups that may be more or less sensitive to the drug, that subgroup's data must also be presented separately.¹¹⁸ In addition to the integrated summary of effectiveness of the drug, the applicant must provide an integrated summary of the benefits and risks of the drug.¹¹⁹ In this section the applicant must explain why the benefits of the drug product exceed the risks under the conditions indicated in the labeling.¹²⁰ If there are any particular risks of the drug product discovered during clinical trials, the proper instructions and warnings must be included in the labeling so that prescribing physicians can use the drug appropriately.

¹¹⁴ Drugs for Human Use, 21 C.F.R. § 314.50(d)(3)(i) (2007).

¹¹⁵ § 314.50(d)(5).

¹¹⁶ § 314.50(d)(5)(ii).

¹¹⁷ § 314.50(d)(5)(v).

¹¹⁸ § 314.50(d)(5)(v). Since drugs may have different effectiveness in each of these subgroups, the applicant must also describe whether there are any dosage modifications needed for a specific subgroup. § 314.50(d)(5)(v).

¹¹⁹ § 314.50(d)(5)(viii).

¹²⁰ Drugs for Human Use, 21 C.F.R. § 314.50(d)(5)(viii) (2007).

In addition to the data collected during the clinical trials, the applicant must submit all relevant information, no matter the source, that is relevant to an evaluation of the safety and effectiveness of the drug.¹²¹ There must be "an integrated summary of all available information about the safety of the drug product."¹²² Information on the safety of the drug includes findings in "animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and . . . epidemiological studies of related drugs."¹²³

The applicant is also required to submit case report forms and tabulations.¹²⁴ Case report forms must be included "for each patient who died during a clinical study or who did not complete the study because of an adverse event" even if the patient was taking a reference drug or placebo.¹²⁵ Tabulations include all data collected during the Phase 1, Phase 2, and Phase 3 investigations.¹²⁶ These tabulations must include data on each patient in each study unless the agency has agreed in advance that a patient's data is "not pertinent to a review of the drug's safety or effectiveness."¹²⁷

3. Chemistry, Manufacturing, and Controls Technical Section

The CMC technical section in the NDA, which is an extension of the CMC in the IND, is where the applicant must indicate the steps it has taken to ensure that there is an effective and uniform manufacturing process and that the ingredients and final product will consistently meet the necessary quality standards. The CMC must convey the specifications that the applicant will

¹²¹ § 314.50(d)(5)(iv).

¹²² § 314.50(d)(5)(vi)(a).

¹²³ § 314.50(d)(5)(vi)(a).

¹²⁴ § 314.50(f).

¹²⁵ § 314.50(f)(2). The case report submission requirement may be waived by the FDA if it feels that the data is unnecessary for review under the circumstances. § 314.50(f)(2).

¹²⁶ Drugs for Human Use, 21 C.F.R. § 314.50(f)(1) (2007).

¹²⁷ § 314.50(f)(1).

require the drug substance to meet.¹²⁸ This includes the quality standards and acceptance criteria necessary to ensure the "identity, strength, quality, and purity of the drug substance and the bioavailability of the drug product" that will be manufactured.¹²⁹ The CMC must also include similar technical information on the final drug product, such as a description of the process controls used in the manufacture of the drug product and the product specifications necessary to assure the "identity, strength, quality, purity, potency, and bioavailability of the drug product."¹³⁰

The production record, specifications and the results of the analytical testing performed on the components and the drug product in the lots used to determine the bioavailability, bioequivalence or stability of the product should also be included in the CMC.¹³¹ With these past production records, there must be a proposed master production record that contains detailed instructions to be used by production and laboratory personnel during the production of each commercial lot of the drug product.¹³² This allows the FDA to compare the initial drug production methods with the proposed final process.

If the FDA so requests, the applicant shall also submit samples of the drug product, the drug substance, reference standards or the finished market package of the drug product.¹³³ The samples may be sent by the FDA to two or more laboratories to perform the quantitative analysis testing as described in the application and validate the methods used by the applicant.¹³⁴ This is the only direct testing that the FDA may perform or require to be performed independently of the applicant.

¹²⁸ § 314.50(d)(1)(i).

¹²⁹ 21 C.F.R. § 314.50(d)(1)(i). A common example of the properties of the drug substance affecting the bioavailability of the drug product would be crystal size. The size of crystals in the drug substance can greatly influence the rate that the drug dissolves or the rate that it is absorbed in the body, depending on the method of drug delivery.

¹³⁰ § 314.50(d)(1)(ii)(a).

¹³¹ § 314.50(d)(1)(ii)(b).

¹³² Drugs for Human Use, 21 C.F.R. § 314.50(d)(1)(ii)(c) (2007).

¹³³ § 314.50(e)(1)(i)-(ii).

¹³⁴ § 314.50(e)(1).

C. FDA Review of NDA Submissions

Throughout the process of reviewing the application, the FDA may communicate with the applicant by any method of communication appropriate to resolve the scientific, medical, or technical question that has arisen.¹³⁵ The FDA will document these communications, between FDA personnel and the applicant, in the application.¹³⁶ If the FDA encounters minor, easily correctable issues, especially in the CMC, it will notify the applicant and allow the applicant to amend the application before the expiration of the review period.¹³⁷ Further, the FDA encourages resolution of disputes between the applicant and the FDA in a manner that is quick, amicable, and based upon the sharing of information.¹³⁸ The FDA has even promulgated regulatory provisions permitting the applicant to suggest that the FDA obtain the advice of an expert to resolve scientific or medical disputes.¹³⁹

The FDA's review of the application is intended to determine whether the drug product has met the statutory standards for safety, effectiveness, manufacturing, and labeling.¹⁴⁰ However, the FDA admits that the statutory requirements apply to all drugs and that some flexibility and scientific judgment are necessary to determine whether the standards are met by different types of drugs with different types of delivery systems that are intended to treat different types of illness.¹⁴¹ The FDA will review an applicant's NDA within the regulatory time limit of 180 days, or within the extended time agreed upon by the applicant, and will send the

¹³⁵ Drugs for Human Use, 21 C.F.R. § 314.102(a) (2007). The FDA also schedules conferences with the applicant at approximately ninety days into the review process and at the end of the review process. § 314.102(c)-(d).

¹³⁶ § 314.102(a).

¹³⁷ § 314.102(b).

¹³⁸ Drugs for Human Use, 21 C.F.R. § 314.103(a) (2007).

¹³⁹ § 314.103(c)(3).

¹⁴⁰ Drugs for Human Use, 21 C.F.R. § 314.105(c) (2007).

¹⁴¹ § 314.105(c).

applicant an "approval letter," an "approvable letter" or a "not approvable letter" at the end of the time period.¹⁴²

The FDA may send an approvable letter at the end of the review period if the NDA is "basically approvable providing certain issues are resolved."¹⁴³ The FDA issues an "approvable letter" if the application substantially complies with its requirements but specific additional information or a specific change is necessary.¹⁴⁴ The FDA will issue a "not approvable letter" if it believes that the application may not be approved for one of the specified reasons for refusal as described below.¹⁴⁵ If none of the stated reasons for refusing approval apply, the FDA will approve an application and send an approval letter.¹⁴⁶ Approval letters are sent only if the deficiencies in the application "concern editorial or similar minor deficiencies in the draft labeling."¹⁴⁷

Under § 314.125(b), there are eighteen reasons for which the FDA can refuse to approve an NDA.¹⁴⁸ The reasons for refusal include FDA findings that: the methods and controls used to manufacture the drug product or substance "are inadequate to preserve its identity, strength, quality, purity, stability and bioavailability" or do not comply with current good manufacturing practice; the manufacturing facilities are not registered with the FDA; there was insufficient testing or information gathered to show that the drug product is safe or the testing did not show that the drug product is safe; there is a lack of information gathered from well-controlled

¹⁴² Drugs for Human Use, 21 C.F.R. § 314.100(a) (2007).

¹⁴³ Drugs for Human Use, 21 C.F.R. § 314.110(a) (2007).

¹⁴⁴ § 314.110(a) (2007).

¹⁴⁵ Drugs for Human Use, 21 C.F.R. § 314.120(a) (2007).

¹⁴⁶ Drugs for Human Use, 21 C.F.R. § 314.105(a) (2007).

¹⁴⁷ § 314.105(b).

¹⁴⁸ Drugs for Human Use, 21 C.F.R. § 314.125(b) (2007).

investigations to show that the drug product is effective for its intended purpose; or the proposed labeling is false, misleading or does not comply with the requirements for labeling.¹⁴⁹

III. CONTINUED FDA MONITORING OF APPROVED DRUG PRODUCTS

The FDA continues to monitor drug products even after approval. The applicant has a continuing obligation to provide information to the FDA about changes to the conditions stated in the NDA, patients' adverse experiences, and production anomalies or changes, all of which may affect the risk-benefit analysis of the drug product.¹⁵⁰ Due to the limited number of patients involved in clinical trials and the limited amount of production experience that the manufacturer will have with the drug product, this continued monitoring is intended to detect emerging dangers associated with the drug product.

A. Amendment of the NDA following FDA Approval

After the FDA approves an NDA, the applicant can still make changes to conditions established in the NDA.¹⁵¹ The level of FDA notification and pre-approval required to implement the change vary, depending on the level of risk the change poses to the product's identity, strength, quality, purity, or potency.¹⁵² The FDA has provided guidance on changes it considers to have substantial potential, moderate potential, and minimal potential to adversely affect the drug product.¹⁵³

The applicant must submit a "prior approval supplement" to the FDA if there is "any change in the drug substance, drug product, production process, quality controls, equipment, or

¹⁴⁹ § 314.125(b)(1)-(18).

¹⁵⁰ See Drugs for Human Use, 21 C.F.R. §§ 314.70-314.71 (2007) (changes from conditions established in NDA); Drugs for Human Use, 21 C.F.R. § 314.80 (2007) (adverse experience reporting); Drugs for Human Use, 21 C.F.R. § 314.81 (2007) (field reports for production anomalies).

¹⁵¹ 21 C.F.R. § 314.71(a) ("Only the applicant may submit a supplement to an approved application.").

¹⁵² U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY, CHANGES TO AN APPROVED NDA OR ANDA, 9-28 (2004).

¹⁵³ *Id.*

facilities that has a *substantial potential* to have an *adverse effect* on the identity, strength, quality, purity, or potency of the drug product."¹⁵⁴ If a supplement to the NDA is necessary, it must contain the sections that would be required in the NDA to support the contemplated change.¹⁵⁵ The FDA must approve the NDA supplement before an applicant can distribute the drug product.¹⁵⁶ In other circumstances, where the change has only a moderate or minimal potential of adversely affecting the drug product, the applicant must submit a supplement to the FDA thirty days before it implements the change.¹⁵⁷

B. Postmarketing Reporting by the Applicant

After the FDA approves the drug product, the applicant is required to continue reporting adverse drug experiences obtained from any source to the FDA.¹⁵⁸ If the applicant does not provide the required reports, there is sufficient reason for the FDA to withdraw its approval of the drug product.¹⁵⁹ Adverse experiences include incidents relating to overdose, drug abuse, withdrawal, or "failure of expected pharmacological action."¹⁶⁰ When an adverse event is both serious and unexpected, the applicant must report the event to the FDA in an alert report within fifteen calendar days.¹⁶¹ Generally, the applicant must provide quarterly periodic reports for the

¹⁵⁴ 21 C.F.R. § 314.70(b)(1). According to § 314.70(b)(2)(i)-(vi), the types of changes that may meet this criteria are: changes in the formulation of the drug, including inactive ingredients; changes requiring studies to determine "equivalence of the drug product to the drug product as manufactured without the change"; changes affecting sterility assurance; changes to the manufacture of the drug substance; certain specified labeling changes; or changes in the closure system, type or composition of packaging that are likely to affect the drug product. § 314.70(b)(2)(i)-(vi).

¹⁵⁵ § 314.71(b).

¹⁵⁶ Drugs for Human Use, 21 C.F.R. § 314.70(b)(3) (2007).

¹⁵⁷ § 314.70(c). The manufacturer cannot distribute the drug or drug product until thirty days after the FDA's receipt of the supplement. § 314.70(c)(5)(i)-(ii).

¹⁵⁸ Drugs for Human Use, 21 C.F.R. § 314.80(b)-(c) (2007).

¹⁵⁹ § 314.80(j). An "adverse drug experience" is defined by the FDA to include "[a]ny adverse event associated with the use of the drug in humans, whether or not considered drug related." § 314.80(a).

¹⁶⁰ § 314.80(a).

¹⁶¹ § 314.80(c)(1)(i)-(iii). A serious adverse drug experience is a drug related experience where the outcome is anything more serious than hospitalization, prolongation of hospitalization, disability or congenital anomaly. § 314.80(a). An unexpected adverse experience is one that is not listed on the current labeling for the drug product, including events "related to an event listed in the labeling" if the event differs because of "greater severity or

first three years after approval, and then annually, for all events that are not reported in a fifteen-day alert report.¹⁶² The periodic reports must contain a summary of the alert reports, an adverse reaction report for each adverse event not reported in an alert report, and a description of the applicant's actions taken over the preceding period as a result of adverse drug experiences.¹⁶³

The applicant, in addition to adverse experience reporting, is required to make postmarketing reports to the FDA, such as annual reports, NDA field alert reports, and copies of the advertisements and promotional labeling.¹⁶⁴ If the applicant fails to make the continued postmarketing reports as described, the FDA has the option of withdrawing its approval of the application and prohibiting marketing of the concerned drug product.¹⁶⁵ Field alert reports must be submitted regarding "any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article," significant "chemical, physical, or other change or deterioration in the distributed drug product," and the "failure of one or more distributed batches of the drug product to meet the specification established for it in the application."¹⁶⁶

C. Withdrawal of FDA approval

The FDA has the authority to withdraw its prior approval of an NDA. The FDA must notify the applicant and provide a hearing if the Secretary of Health and Human Services suspends approval "on a finding that there is an imminent hazard to the public health" or if the FDA finds that the clinical investigations or other scientific evidence "show that the drug is unsafe for the intended use," or that any part of the application contains an untrue statement of

specificity." § 314.80(a). The adverse experience is still considered "unexpected" if it was predicted by the pharmacologic studies but has not been observed in trials or included on the labeling of the drug. § 314.80(a).

¹⁶² § 314.80(c)(2)(i). In this section, the FDA retains authority to alter the due dates of periodic reports.

¹⁶³ § 314.80(c)(2)(ii).

¹⁶⁴ Drugs for Human Use, 21 C.F.R. § 314.81(b)(1)-(3).

¹⁶⁵ § 314.81(d).

¹⁶⁶ § 314.81(b)(1)(i)-(ii). These alert reports must be submitted to the FDA district office responsible for the facility within three working days. § 314.81(b)(1).

material fact.¹⁶⁷ The FDA may also notify the applicant and provide a hearing to withdraw approval if the applicant fails to establish an appropriate recordkeeping system or make the appropriate reports to the FDA; if there is new information that the methods or controls on manufacturing are inadequate to ensure that the drug product consistently meets its specification; if there is new information that the labeling is false or misleading; or if there were any investigations that were not carried out according to the regulations or were omitted from the application.¹⁶⁸ The FDA can even withdraw approval without a hearing if the applicant consents to withdrawal from the market.¹⁶⁹

IV. LEGISLATIVE EVALUATION OF THE FDA APPROVAL PROCESS

When viewing a description of the FDA approval process for drug products, it may appear that the agency performs a complete and thorough scientific evaluation and that all possible aspects of review are addressed by the agency. However, legislatures should look more deeply at the FDA review process to evaluate whether the assumptions that usually motivate tort liability protection are warranted in the context of FDA-approved drugs. Generally, the assumptions underlying tort protection for drug manufacturers are: the FDA has concluded a drug product is safe when it approves the drug product; the FDA has performed a thorough, independent review of the drug product to evaluate its scientific merits; and limitation or elimination of tort liability will encourage development and release of additional drugs as well as lower drug prices. Although the FDA approval process is scientifically rigorous, there are several factors that undermine these assumptions in the context of drug manufacturers, such as

¹⁶⁷ Drugs for Human Use, 21 C.F.R. § 314.150(a)(1)-(2) (2007).

¹⁶⁸ § 314.150(b)(1)-(10).

¹⁶⁹ § 314.150(c)-(d).

the FDA's reliance on the drug manufacturers, the unique nature of pharmaceutical products, and the inability of the clinical investigations and continued monitoring to detect all drug risks.

A. Rigor of the FDA Approval Process

The FDA approval process is time consuming, expensive, and scientifically based. The FDA is an experienced governmental agency with a high degree of expertise in the pharmaceutical industry and the process it has designed is clearly intended to reveal the scientific merits of a drug prior to its commercial release. The process begins with pharmacology and toxicology testing to determine whether the drug meets a threshold level of safety before it is administered to human subjects. The process continues through clinical investigations, requiring higher levels of scientific justification to continue with each step of the approval process. Overall, the FDA's approval process is rigorous, and it does ensure that there is a significant quantity of scientific data available on a drug product before it is commercially released.

The FDA has enacted rules requiring that the clinical investigations of the drug be carried out in accordance with the scientific method. Rules governing Phase 2 and Phase 3 of the clinical investigations, especially, require scientifically adequate and well-controlled studies. These investigations must have a protocol describing the study to be conducted, a study plan that is consistent with recognized scientific methods of evaluation, and a post-study report analyzing the results of the study. These requirements are consistent with respected scientific methods of experimentation and are well suited to discovering the effectiveness of a drug product and its side effects. These tests also control what labeling will be required to accompany the drug when it is marketed to the public. This scientific method of testing allows the manufacturer or the investigator to keep a thorough record of the side effects that are reported during the investigations so that the warnings present on the labels are supported by sufficient evidence.

Further, the FDA has recognized that adequate and well-controlled investigations also require the drug product being tested to be consistent. CMC sections are required in each IND and in the final NDA to show that the drug product manufactured and tested in each stage of development was consistently produced, and was of the same identity, strength, quality, and purity as the drug produced during the last round of evaluation. This standardization permits a more thorough comparison throughout the different stages of approval and the different production methods that are likely to be used. The requirements for manufacturing controls are also of primary importance because impurities in the drug product may be harmful and because difference in the dose of the drug that is delivered to patients may be dangerous.

Even after a drug product has been approved, the FDA requires continued monitoring of the drug product to ensure that long-term side effects and rare side effects of the drug are discovered and that a continuing evaluation of the risks and benefits of the drug can be undertaken. If information is discovered which causes the FDA to change its benefit-risk assessment, it even has the authority to withdraw its previously granted approval.

At several points throughout the process, the FDA also requires information not just on the drug product, but also on the people who will be administering the tests and drawing conclusions from the data. The FDA obtains this information so that it can verify that the people responsible for decisions regarding the current and future testing of the drug product have the appropriate qualifications, and also that they are not improperly financially motivated.

For all of these reasons, drug manufacturers should be entitled to some level of protection from tort liability. Their drug products have been extensively tested to obtain FDA approval. Further, the FDA is has had the ability to review all of the clinical investigation data and data collected during continued monitoring and has concluded that the label warnings are adequate.

B. FDA Reliance on Drug Manufacturer

The FDA relies heavily on the drug manufacturer throughout the entire new drug approval process. It is the drug manufacturer who identifies potential products and performs the preliminary safety analysis, designs clinical investigations and selects investigators, administers or monitors the clinical investigations, summarizes all of the data for the FDA to review, and explains the benefits and risks of the drug product to the FDA. The FDA drug-approval process is generally a process that obligates the manufacturer to supply information to the FDA. The FDA does not have the manpower to investigate each submission for accuracy or integrity, and the entire system is designed to work through manufacturer cooperation with the agency's requirements. The FDA's reliance on the drug manufacturer and its findings are evidenced by FDA rules which encourage meetings between the FDA and the drug sponsors to resolve scientific problems and assist in the drug's evaluation "to the extent that FDA's resources permit" on the theory that there should be "free, full, and open communication" about scientific and medical issues.¹⁷⁰

Additionally, the FDA extensively regulates clinical investigations, which form the basis for both approval and labeling decisions, but it does not perform any of the investigations on its own.¹⁷¹ The FDA relies on the applicant to design scientifically adequate and well-controlled clinical investigations, perform those investigations, and then present all of the necessary data to the FDA. It is also the applicant who presents an integrated summary of the drug's benefits and

¹⁷⁰ Drugs for Human Use, 21 C.F.R. § 312.47(a) (2007). The FDA recommends drug sponsors meet with agency personnel at the end of Phase 2 studies and again before the NDA is submitted. § 314.47(b).

¹⁷¹ The only testing that the FDA may request an independent laboratory perform is the analytical testing of the drug product itself to determine its identity, strength, quality, and purity. *See* Drugs for Human Use, 21 C.F.R. § 314.50(e)(1) (2007).

its risks. Additionally, the applicant is required to submit significant quantities of summary information regarding other areas of the NDA for the FDA to review.¹⁷²

This level of reliance on the NDA applicant's scientific judgment, when the applicant's goal is to sell the drug commercially, is somewhat surprising considering the potential danger that is presented by drug products. Even without defrauding the FDA, the manufacturer has the ability to "spin" the data and the way that it is presented to the FDA. This is not to say that all, or even most, drug manufacturers would attempt to "spin" data. However, the ability of drug manufacturers to present clinical investigation data in its most favorable light, or even bury non-favorable results amidst hundreds or thousands of pages of data in an NDA, undercuts one of the basic assumptions underlying tort liability protection. It is not necessarily true that the FDA has reviewed the drug thoroughly and independently on its scientific merits before approving the drug when the FDA is relying heavily on the manufacturer to find and then point out any potential dangers resulting from use of the drug product.

Furthermore, even when the drug manufacturer and its investigators have clearly been dishonest with the FDA, the FDA has still relied on the results that it was presented. During the approval of Ketek, an antibiotic used to treat minor conditions such as sinus infections, the FDA asked the manufacturer to perform an additional safety study due to FDA concern of serious, and potentially deadly, side effects.¹⁷³ When the FDA reviewed the supplemental study, the "routine FDA inspection of the practices of the physician who enrolled the most patients . . . uncovered fraud, including complete fabrication of patient enrollment."¹⁷⁴ The FDA inspectors also found evidence of serious violations by other investigators.¹⁷⁵ Even though the FDA managers were

¹⁷² § 314.50(c)(2)

¹⁷³ David B. Ross, M.D., Ph.D., *The FDA and the Case of Ketek*, 2007 NEW ENG. J. MED., 2007 1601, 1601.

¹⁷⁴ *Id.* at 1601-02.

¹⁷⁵ Ross, *supra* note 173, at 1602.

actually aware of the improprieties in the investigations, the FDA relied on the study in its decision to approve Ketek.¹⁷⁶

In addition to the reliance on the drug manufacturers for the provision of pre-approval information, the FDA may also rely on the promise of a drug manufacturer that further clinical investigations will be conducted once the drug has been approved for marketing.¹⁷⁷ However, 71% of the postmarketing clinical studies that manufacturers have agreed to conduct have not yet been started and the "FDA has difficulty forcing the companies to conduct those studies" which they have already agreed to undertake.¹⁷⁸

There may be cases where the manufacturer's conduct has not sunk to the level of noncompliance, but the manufacturer has simply taken an optimistic view of the benefits its newly developed drug will provide and has highlighted this view in its application materials. Although this is not technically against the FDA's rules, legislatures should consider whether the FDA is appropriately staffed and trained to spot such subjective evaluations of a drug product. Further, there are examples indicating that, despite the fact that many manufacturers attempt to comply with every requirement for FDA approval, sometimes drug manufacturers do not comply. Although there may be egregious cases of noncompliance, there may also be cases where the manufacturer has simply not begun further evaluations according to schedule. Legislatures should be especially vigilant in evaluating whether the FDA approval process has sufficient safeguards to detect such noncompliance, and whether the FDA is appropriately funded to fully investigate and appropriately prosecute these cases.

¹⁷⁶ Ross, *supra* note 173, at 1602-03.

¹⁷⁷ Donna Young, *Regulatory Experts Debate FDA's Authority*, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, May 1 2007, http://www.ashp.org/s_ashp/article_news.asp?CID=167&DID=2024&id=19783.

¹⁷⁸ *Id.*

C. Unique Nature of Pharmaceutical Products

Drug products are unlike traditional goods. When a drug product is operating exactly as intended, there may be both beneficial treatment of disease *and* undesirable side effects.

Therefore, there is always a balancing that must be undertaken to evaluate whether the drug's beneficial effect on disease is sufficient to outweigh the side effects of the drug.

When the FDA approves a drug for marketing and use by the public, it is determining that the benefits of the drug outweigh the drug's known risks. Special regulations governing the use of drugs intended to treat serious or life-threatening diseases are illustrative of the agency's policy-driven balancing act for approval of new drugs. For these drugs, the FDA permits patient treatment use much earlier in the clinical investigation stages, as early as Phase 2 of the clinical investigation.¹⁷⁹ Treatment use is permitted only when there is no "comparable or satisfactory alternative drug or other therapy."¹⁸⁰

This practice reflects the FDA's general risk-benefit balancing approach. In the case of patients who have a serious or immediately life-threatening disease, the FDA's rules reflect a judgment that the potential for unknown and incompletely studied risks do not outweigh the potential benefits of the drug treatment. In the case of less serious diseases, the more intensive investigative and clinical study requirements indicate that the FDA has determined the potential for risk must be more thoroughly studied before a risk-benefit analysis can be appropriately performed.

The FDA also expressly reserves the right to use flexibility and scientific judgment to determine whether waivers should be provided to the manufacturer for NDA or postmarketing

¹⁷⁹ Drugs for Human Use, 21 C.F.R. § 312.34(a) (2007).

¹⁸⁰ § 312.34(b)(ii).

reporting requirements.¹⁸¹ This flexibility is, no doubt, necessary in some cases due to the broad scientific differences between different drug products and because of the various diseases and conditions that drug products are intended to treat. However, such broad discretion creates an opportunity for the applicant to perform a less rigorous scientific review and still obtain FDA approval.¹⁸² The necessity of using a balancing test and this flexibility in FDA requirements reveals that when the FDA has approved a drug product, it has not determined that the drug product is necessarily "safe." The approval decision is always based on the current state of scientific knowledge and on the benefits and risks as they have been presented to the FDA and discovered through the clinical investigations. State legislatures should take this into consideration when determining how to treat FDA approval in the tort context.

D. Limited Clinical Investigations and Time Lag Before Withdrawal

To further complicate the FDA's approval decisions, and the legislative decision how to treat FDA approval, the FDA must evaluate policy concerns to determine what labeling is appropriate and to determine what quantity of premarket testing will be sufficient. In balancing the relevant policy considerations the FDA has demonstrated a preference for including warnings only for scientifically provable side effects on the labeling so that physicians will not be deterred from prescribing a drug product by unproven side effects.¹⁸³ Because of this policy, there is a debate over the quantity of testing required to explore the drug's side effects.

¹⁸¹ Drugs for Human Use, 21 C.F.R. § 314.90(b)(1)-(3) (2007).

¹⁸² The FDA's discretion in this matter is bounded, by the requirements under 21 C.F.R. § 314.90(b) that there must be a justification for the waiver or that the purpose of the requirement is met. Yet, the FDA's discretion is still significant.

¹⁸³ Viscusi et al., *The Effect of Products Liability Litigation on Innovation: Deterring Inefficient Pharmaceutical Litigation: an Economic Rationale for the FDA Regulatory Compliance Defense*, 24 SETON HALL L. REV. 1437, 1463 (1994) (citing 44 Fed. Reg. 37,434, 37,431 (1979) ("The act permits labeling statements with respect to safety only if they are supported by scientific evidence . . .")).

There are incentives for the FDA to require substantial premarket testing. More substantial testing, either in number of patients or length of time, is statistically more likely to detect drug side effects that are rare or that only develop over time. The FDA is likely to ensure that drugs are safer or at least that a more complete listing of the possible effects of the drug are available with increased investigation. However, there are also policy incentives for the FDA to approve drugs quickly, with less scientific testing. If the drug will provide treatment for disease, the population will be benefited if they are able to take the drug to treat that disease. A shorter investigation with fewer patients is also likely to cost manufacturers less money and may encourage more investment in drug development by pharmaceutical companies.

The combined number of patients tested during clinical trials may be only a few thousand¹⁸⁴ and the duration of the studies may be limited. When this abbreviated amount of testing is required, there are many side effects or drug interactions that will not be discovered. This is one reason that continued adverse event reporting is required even after drug product approval, so that the FDA can stay informed about emerging evidence of side effects. In the days when new drugs were prescribed slowly at first, and then gradually with increasing frequency, continued reporting was likely more effective at catching emerging evidence of side effects. However, with the current environment of heavy direct-to-consumer advertising and "blockbuster" drugs, many drug products are prescribed widely shortly after approval and by the time adverse experiences are reported, there are many more patients who have already been exposed to the dangers of the drug product.

¹⁸⁴ According to FDA regulations, there may be less than 100 patients tested during Phase 1, a few hundred patients tested during Phase 2, and a few thousand patients tested during Phase 3. Drugs for Human Use, 21 C.F.R. § 312.21(a) (2007) (Phase 1); Drugs for Human Use, 21 C.F.R. § 312.21(b) (2007) (Phase 2); Drugs for Human Use, 21 C.F.R. § 312.21(c) (2007) (Phase 3).

Even if there is evidence discovered through the continued monitoring of the drug that the benefit-risk analysis has changed, it may take a significant amount of time for the FDA to withdraw its approval of a drug product. The FDA is a large and complex governmental agency, and its reactions are not necessarily swift. In the case of fenfluramine and dexfenfluramine, half of the famous phen-fen duo, the first report of heart disease was made to the FDA on July 8, 1997, and it included twenty-four patients who were suffering from serious heart valve disease.¹⁸⁵ The FDA's approval was not withdrawn until September 15 of that year, nearly two months later.¹⁸⁶ What is surprising about this length of time is that there was a very serious reaction and the manufacturer *agreed* to remove the drug without a hearing.¹⁸⁷ In other cases, such as the review of the drug Ketek, it took the FDA sixteen months from the first reported death to re-label the product so that patients would be warned of serious side effects.¹⁸⁸ In the meantime, many patients were exposed to the severe dangers of the antibiotic. Furthermore, although the FDA has the authority to withdraw its approval for a drug product, it is generally required to provide a hearing before withdrawal unless the manufacturer consents to the withdrawal of the drug from the market.¹⁸⁹ The requirement for a hearing prior to withdrawal may create an even longer delay before the approval may be withdrawn.

Moreover, the FDA is an executive agency, and is arguably responsive to political pressures. In the 1980's, there was considerable public criticism of the slow approval process. Since that time, the FDA has implemented measures in an attempt to streamline and speed the NDA approval process. Recently, there has even been controversy over the approval of a

¹⁸⁵ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *Questions and Answers About Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux)*, <http://www.fda.gov/cder/news/phen/fenphenga2.htm>.

¹⁸⁶ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *supra* note 185.

¹⁸⁷ U.S. Food and Drug Administration, Center for Drug Evaluation and Research, *supra* note 185.

¹⁸⁸ Ross, *supra* note 173, at 1603.

¹⁸⁹ *See infra* Part IV.C.

particular drug, the "Plan B" contraceptive pill. FDA Assistant Commissioner and Director of the Office of Women's Health, Susan F. Wood, reportedly resigned following the Commissioner's intervention and refusal to approve the "morning after" pill for over-the-counter use despite the clinical testing, which had shown the product to be appropriately safe and effective for its intended purpose.¹⁹⁰ In that case, there were accusations that the political considerations did not just influence a borderline balancing decision, but actually caused the Commissioner to veto a scientific decision made by FDA Examiners.¹⁹¹ It is conceivable that outside pressures could work in the opposite direction as they did in relation to Plan B, and could encourage the FDA to approve a drug of doubtful effectiveness or safety because there is political pressure to do so.

The amount of clinical investigation required for drug products prior to approval rests on a policy decision made by the FDA, and the testing is quite obviously not capable of detecting all side effects that will be discovered when the drug is released to the general public. However, the FDA permits only those side effects that are supported by scientific evidence to be present on the labeling. Further, the balancing nature of the drug approval process allows outside pressures to more easily influence the FDA's decision on drug product approval. These factors are also important for legislatures to consider when determining how drug product labeling should be evaluated for purposes of tort liability, and they should evaluate whether these factors undercut the presumption that the FDA has performed a thorough and independent review of the drug based on its scientific merits.

¹⁹⁰ Marc Kaufman, *FDA Official Quits Over Delay on Plan B: Women's Health Chief Says Commissioner's Decision on Contraceptive Was Political*, <http://www.washingtonpost.com/wp-dyn/content/article/2005/08/31/AR2005083101271.html>.

¹⁹¹ Marc Kaufman, *FDA Official Quits Over Delay on Plan B: Women's Health Chief Says Commissioner's Decision on Contraceptive Was Political*, <http://www.washingtonpost.com/wp-dyn/content/article/2005/08/31/AR2005083101271.html>.

V. STATE HANDLING OF FDA APPROVAL

Several states have already enacted statutes addressing the treatment of FDA-approved drug products in state law failure to warn claims. There are many legal options for states to consider, but it is critical for state legislatures to maintain perspective on the actual implications of FDA approval and the assumptions that are inherent in a decision to provide protection to drug manufacturers. Since FDA approval does not mean that the FDA has evaluated the drug product and found it to be safe, or even found that the current list of side effects is complete, providing a complete defense against a failure to warn tort suit may be problematic. However, since the FDA drug approval process is so highly regulated, providing the manufacturer with no protection from tort liability may also be an undesirable solution.

A. Existing State Treatment of FDA-Approved Drug Products

The Michigan legislature has enacted a statute providing drug companies immunity in failure to warn tort suits when the FDA has approved the drug at issue.¹⁹² There are some exceptions in the statute, such as when the manufacturer intentionally misled the FDA causing the FDA to approve a drug product or when there has been bribery of an FDA official, i.e., fraud on the FDA or bribery.¹⁹³ However, under the current case law interpreting the Michigan statute, federal law preempts state claims of fraud on the FDA.¹⁹⁴ The practical effect of these rulings is that, in order to bring a tort suit against a drug company, a Michigan patient must convince the FDA to bring an enforcement suit against the drug company so that the plaintiff can meet the

¹⁹² MICH. COMP. LAWS ANN. § 600.2946(5) (West 2007).

¹⁹³ *Id.*

¹⁹⁴ *Buckman Co. v. Pls. Legal Comm.*, 531, U.S. 341 (2001); *see also Garcia v. Wyeth-Ayerst Labs.*, 384 F.3d 961, 967 (6th Cir. 2004) (state torts requiring proof of fraud against the FDA are preempted by federal law).

exception in the Michigan statute. This rule bars even meritorious claims from proceeding as long as the FDA has approved the drug and has not successfully pursued an enforcement suit.¹⁹⁵

Furthermore, the FDA, even if it chooses to bring an enforcement suit against a drug manufacturer for fraud, will bear a heavy burden of proof. In a fraud suit the FDA must show a causal link between the misstatement or omission in the NDA and the approval of the drug¹⁹⁶ in addition to proving that the manufacturer intentionally inserted or omitted the statement. This can be contrasted with a case where the FDA would have to prove only that there was a material omission or misstatement, but did not have to prove the causal effect on the decision to approve the drug product. In light of the voluminous NDA applications that are submitted, and the balancing that is undertaken by the FDA in its approval decision, this heightened showing will generally be difficult for the FDA to make.

One of the policy justifications attributed to the Michigan legislature, in addition to those previously mentioned, is a fear that tort suits will cause drug manufacturers to build the cost of tort suits into the price of pharmaceuticals and will discourage new drug development.¹⁹⁷ However, even if this is true, and only one state out of fifty enacts such a rule, the result may just be unfair to that state's residents. It is much more likely that drug manufacturers are building the cost of tort suits in forty-nine states into the cost of the drugs and taking it into account in drug development systems.

There is no evidence that, since the enactment of this statute, drug prices have fallen in Michigan, that drugs have been made available in Michigan that are not available in other states,

¹⁹⁵ Interestingly, under the wording of the Michigan statute, the manufacturer of a drug that is approved by the FDA is protected, regardless of whether the manufacturer has fully complied with all FDA requirements. It appears that if the FDA revokes approval of the drug for failure to comply with the postmarketing requirements, a party who was injured before the revocation is still unable to bring a claim in Michigan. *See* § 600.2946(5).

¹⁹⁶ *Buckman Co.*, 531 U.S. at 353 (Stevens, J., concurring).

¹⁹⁷ *Wyeth-Ayerst Labs.*, 384 F.3d at 967.

or that pharmaceutical companies are moving into Michigan to manufacture their products. Further, there are significant incentives for drug companies to price their products nationally, not least of which are the Medicare and Medicaid systems run by the federal government. Under each of these systems, the federal government has significant purchasing power that it exercises nationally. Therefore, it is unlikely that drug prices would be lowered in Michigan in response to the tort liability protection or that drugs would be made available only in Michigan. Additionally, since the legislature enacted the statute providing immunity, large pharmaceutical manufacturing companies have sold or closed their plants in Michigan. Michigan residents may be paying the price of tort liability without the benefit of being able to bring their own tort claims.

At the opposite end of the spectrum from Michigan are states that do not provide any level of statutory protection to the manufacturer of a pharmaceutical product other than the same protections that are provided to all manufacturers.¹⁹⁸ This policy answer also seems too extreme. After all, pharmaceutical manufacturers are making a type of product that is entirely different than other goods, they are required to extensively test their products in order to create the warnings that must appear on the labeling, and the manufacturers are not allowed to add warnings of side effects to the labeling without FDA approval.¹⁹⁹ In light of the potential emergence of previously unknown side effects when the drug is marketed to the public and the drug manufacturer's lack of freedom to label the product as it wishes, some protection from failure to warn tort suits is warranted.

¹⁹⁸ *E.g.*, New Hampshire. *See supra* notes 5, 8 and accompanying text.

¹⁹⁹ Technically, there are some types of warning that can be added to the label prior to FDA approval. *See* 21 C.F.R. §§ 314.70(c), 601.12(f)(2). However, FDA approval must be sought after the inclusion, and if the FDA does not approve of the labeling change, it can bring an enforcement action against the drug manufacturer for adulteration or mislabeling of the drug. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3968-69 (Jan. 24, 2006). The practical effect is that drug manufacturers will seek FDA approval prior to changing a drug product's labeling. *Id.*

Between these two extremes, there are states that provide intermediate levels of protection to drug manufacturers. States providing intermediate levels of protection have created several different solutions to the policy debate over failure to warn tort suits. Some states use a statutorily-prescribed rebuttable presumption that the label provides sufficient warning when the FDA has approved the relevant drug product.²⁰⁰ Other states bar punitive damages if the FDA has approved the drug product and its labeling.²⁰¹ Some states have also provided an extra degree of protection to the drug manufacturers by requiring the plaintiff to present clear and convincing evidence to rebut the presumption or to show that the manufacturer misled the FDA.²⁰²

States that provide intermediate levels of protection have come to different policy balances than the Michigan legislature. The methods used by these states are intended to similarly limit the number of suits brought against drug manufacturers and to limit the amount of damages awarded in failure to warn tort suits. Yet, the state legislatures have indicated that a meritorious plaintiff's claim should be permitted to proceed or that a plaintiff who has suffered actual harm from a drug product should be permitted to recover at least the actual damages suffered.

B. Proposed Treatment of FDA-Approved Drug Products

As some state legislators have determined, there are valid reasons to treat compensatory and punitive damages differently. Compensatory damages are only those damages intended to make the plaintiff whole and replace what the plaintiff has lost.²⁰³ With regard to compensatory damages, a reasonable solution would be to legislate a rebuttable presumption that an FDA-

²⁰⁰ N.J. STAT. ANN. § 2A:58C-4 (West 2007); TEX. CIV. PRAC. & REM. CODE ANN. § 82.007(a) (2006).

²⁰¹ N.J. STAT. ANN. § 2A:58C-5(c) (West 2007); OHIO REV. CODE ANN. § 2307.80(C)(1) (West 2007); OR. REV. STAT. ANN. § 30.927 (West 2007); UTAH CODE ANN. § 78-18-2 (West 2007).

²⁰² OR. REV. STAT. ANN. § 30.730(1) (West 2007); UTAH CODE ANN. § 78-18-2 (West 2007).

²⁰³ BLACK'S LAW DICTIONARY 394 (7th ed. 1999).

approved drug product and its associated labeling cannot be the basis for a failure to warn products liability suit. Such a presumption would, ideally, create a heavy burden for a potential plaintiff. For the FDA to approve a drug product, the manufacturer must have shown considerable evidence that it is effective for the label indications and that the manufacturer has sought to discover information on the risks to include in the labeling.

In order to overcome the showing that the manufacturer must have made and the expert opinion of the FDA, the plaintiff should be required to make a clear and convincing showing that the manufacturer knew or should have known of the risk that the plaintiff suffered at the time of the drug's sale. Placing the burden squarely on the plaintiff to rebut a presumption in the drug manufacturer's favor may, procedurally, lead to the disposition of many plaintiff's cases through summary judgment. However, this would accomplish the desired objective of protecting drug manufacturers to the extent the manufacturers have properly sought approval for their drug products.

The burden on a plaintiff challenging an FDA-approved drug should be heavy. However, the opportunity to obtain compensatory relief should not be completely foreclosed. As previously described, there are several reasons why the FDA's decision to approve a drug does not necessarily lead to the conclusion that a drug product is safe for public use. An FDA finding that the manufacturer has defrauded the FDA in the approval process or during postmarketing reporting in a manner that is relevant to the claimed injury should clearly be sufficient to rebut the presumption.²⁰⁴ However, state legislatures should also permit plaintiffs to provide other evidence that the manufacturer was aware of the risks and failed to adequately warn patients of

²⁰⁴ See *Wyeth-Ayerst Labs.*, 384 F.3d at 967; Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3933-34 cmt. 13 (Jan. 24, 2006) (stating FDA's position that its regulations trump state law). Since federal law preempts state law, then a finding under federal law should be fully enforced by the state tort system.

those risks. For example, if there are serious dangers revealed by the nonclinical testing or suggested by reports of adverse experiences and the manufacturer has taken no action or has not fully complied with the FDA's notification requirements, the plaintiff should be permitted to present such evidence to rebut the presumption in the manufacturer's favor.

Further, there may be plaintiffs who began taking the drug product after evidence was discovered to justify a hearing and withdrawal of FDA approval. These patients may take the drug product during the entire time period between when the evidence is discovered and the FDA's eventual withdrawal of approval. If the presumption is effective for drugs sold while they have an FDA-approved status, these patients may be left without recourse unless the evidence that justified the eventual withdrawal of the drug product is also found to be sufficient to rebut the presumption in the manufacturer's favor. When the evidence warranting withdrawal of FDA approval has been discovered, the assumptions that normally motivate tort liability protection are not applicable. Both the FDA and the manufacturer are aware of the drug product's risk and that risk is not communicated to patients.

Punitive damages, in contrast to compensatory damages, are intended to provide an extra level of punishment "when the defendant acted with recklessness, malice, or deceit."²⁰⁵ Punitive damages are often dramatically large in order to operate as a deterrent for the manufacturer found at fault and for other manufacturers. Such damages should be much more difficult for a plaintiff to obtain than compensatory damages for actual injury suffered. If the manufacturer has designed a plan that meets the scientific standards of the FDA, it seems highly unlikely that the manufacturer has acted egregiously enough to warrant the imposition of punitive damages unless the manufacturer has intentionally misled or deceived the FDA.

²⁰⁵ BLACK'S LAW DICTIONARY 396 (7th ed. 1999).

However, there is popular sentiment that if a drug causes serious side effects, the large and sophisticated drug manufacturer must have known about the potential side effect in advance. Further, if a tort case gets as far as the trial stage, there will clearly be a patient who has been harmed by the drug product. No matter how unlikely the side effect or how unexpected beforehand, the potential may seem obvious after it has occurred. After there is a conclusive finding, it might also be easier to review the research and find cases that, in hindsight, make the danger apparent. Therefore, state legislatures should only permit punitive damages following an FDA finding that the drug's sponsor deceived or intentionally misled the FDA or committed some other form of fraud to ensure that the drug was approved or to ensure that the FDA did not discover later-emerging side effects. This will prevent judges and juries from second-guessing the FDA or drug manufacturers in their area of scientific expertise.

This intermediate approach, in regard to both compensatory and punitive damages, is intended to take into account the practical realities of FDA approval. Presumptions in the manufacturer's favor reveal the legislature's recognition that the FDA approval process does require significant scientific testing of drug products and that the FDA is an expert agency that is better situated than a jury to evaluate the risks and benefits of the drug product. However, making the assumption rebuttable demonstrates recognition that the FDA balancing process is generally undertaken with incomplete information and information supplied primarily by the manufacturer who intends to commercially market the drug. Further, elimination of punitive damages will help to reduce potentially large awards and will help to ensure that drug manufacturers are not deterred from developing new and innovative drug products by the threat of dramatically large damage awards.

CONCLUSION

FDA regulations are intended to ensure that drug manufacturers perform scientifically adequate investigations to prove their drug products' efficacy for the claimed indications and to discover its side effects. The FDA specifically requires that only side effects supported by scientific evidence can be included on drug product labeling and the FDA uses its scientific and pharmaceutical expertise to determine the appropriate label warnings.

Due to the premarketing research that is performed and the FDA's control over the labeling, manufacturers deserve some protection from failure to warn tort suits. This protection should be provided by state legislatures after they have evaluated the scientific merits of the FDA approval process and the relevant policy concerns, rather than leaving courts to decide on a case-by-case basis. An intermediate level of protection for drug manufacturers is a reasonable approach, and state legislatures can use combinations of presumptions, burdens of proof, and bans on punitive damages to attempt to ensure that meritorious plaintiffs are permitted to proceed and recover compensatory damages while still providing a significant level of protection for the manufacturers of FDA-approved drugs.